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Metalaxyl and Mefenoxam
Summary Document
Registration Review: Initial Docket
December 2009

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Case # 0081

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Date

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Please Note

This Preliminary Work Plan and Fact Sheet summarize the Environmental Protection Agency's current position based on the following documents:

1. *Registration Review–Preliminary Problem Formulation for Environmental Fate, Ecological Risk, and Endangered Species for metalaxyl (PC Code 113501) and Mefenoxam (aka metalaxyl-M, PC Code 113502).* August 27, 2009.

2. *Metalaxyl/Mefenoxam: Human Health Assessment Scoping Document in Support of Registration Review.* December 7, 2009.

3. *Metalaxyl Screening Level Usage Analysis (SLUA).* April 7, 2009.

4. *Mefenoxam Screening Level Usage Analysis (SLUA).* May 5, 2009.

5. *Updated Review of Metalaxyl Incident Reports.* June 11, 2009.

6. *Updated Review of Mefenoxam Incident Reports.* July 7, 2009.

The supporting documents for metalaxyl and mefenoxam may be found in docket EPA-HQ-OPP-2009-0863, located on the internet at www.regulations.gov.

I. PRELIMINARY WORK PLAN – Metalaxyl and Mefenoxam Registration Review

Introduction

The Food Quality Protection Act (FQPA) of 1996 mandated a registration review program**.** All pesticides distributed or sold in the United States generally must be registered by the Environmental Protection Agency (EPA or the Agency), based on scientific data showing that they will not cause unreasonable risks to human health or the environment when used as directed on product labeling. The registration review program is intended to make sure that, as the ability to assess risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects to human health or the environment. Changes in science, public policy, and pesticide use practices will occur over time. Through the registration review program, the Agency periodically reevaluates pesticides to make sure that as change occurs, products in the marketplace can be used safely. Information on this program is provided at: http://www.epa.gov/oppsrrd1/registration_review/.

The Agency is implementing the Registration Review program pursuant to Section 3(g) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and will review each registered pesticide every 15 years to determine whether it continues to meet the FIFRA standard for registration. The Agency will consider benefits information and data as required by FIFRA. The public phase of registration review begins when the initial docket is opened for each case. The docket is the Agency's opportunity to state what it knows about the pesticide and what additional risk analyses and data or information it believes are needed to make a registration review decision. After reviewing and responding to comments and data received in the docket during this initial comment period, the Agency will develop and commit to a final work plan and schedule for the registration review of metalaxyl and mefenoxam.

Metalaxyl and mefenoxam are systemic fungicides that are registered for use to control foliar (plant) and soil diseases caused by certain types of fungi. Metalaxyl and mefenoxam may be used as foliar, soil, or seed treatments for agricultural crops or as a treatment in the residential environment. Currently, both metalaxyl and mefenoxam are registered for use on a wide variety of fruit, vegetable, and feed crops, including both field crops and orchards, and have several nonfood ornamental uses as well, including lawns, golf courses, and nurseries. Mefenoxam also has a forestry use. Metalaxyl was first registered in the U.S. in 1979, and mefenoxam was first registered in the U.S. in 1992.

These two active ingredients are being addressed together in the same registration review case because they are both mixtures of the same two enantiomers. Metalaxyl is a mixture that is composed of approximately equal proportions of the *R* and *S* enantiomers, whereas mefenoxam is an enrichment comprised almost solely of the *R* enantiomer. A synonym for mefenoxam is metalaxyl-M.

Anticipated Risk Assessment and Data Needs

The Agency anticipates conducting an ecological risk assessment of metalaxyl and mefenoxam, including an endangered species assessment. The Agency also anticipates conducting human health risk assessments for metalaxyl and mefenoxam. Below is a summary of the issues relevant to the registration review of metalaxyl and mefenoxam.

Ecological Risk:

- An environmental fate and effects risk assessment for metalaxyl was completed in support of the 1994 metalaxyl Reregistration Eligibility Decision (RED). In that assessment, the Agency found no risks of concern.

- In 2001, ecological assessments for mefenoxam were also conducted for proposed new uses on canola seed and on several fruits, vegetables, and herbs. In these assessments, the Agency found potential acute risks of concern for mammals, including to threatened and endangered species. The Agency found no other risks of concern.

- The Agency has not conducted a risk assessment that supports a complete endangered species determination. The ecological risk assessment planned during registration review will allow the Agency to determine whether metalaxyl's and mefenoxam's uses have "no effect" or "may affect" federally listed threatened or endangered species (listed species) or their designated critical habitats. When an assessment concludes that a pesticide's use "may affect" a listed species or its designated critical habitat, the Agency will consult with the U.S. Fish and Wildlife Service and/or National Marine Fisheries Service (the Services), as appropriate.

- Results from previous toxicity studies indicate that Typical End-use Products (TEP) containing metalaxyl are generally more toxic than the technical grade active ingredient (TGAI) for all aquatic organisms other than mollusks. Therefore, the Agency anticipates requiring additional aquatic toxicity data not only on TGAIs, but also on TEPs. The Agency anticipates using these data to conduct acute risk assessments to nontarget aquatic animals for exposure to TEPs as well as for exposure to TGAIs.

- EPA anticipates requiring the following guideline data in order to conduct the planned environmental fate and ecological risk assessments for the registration review of metalaxyl and mefenoxam:
    - 850.2100 Avian Acute Oral, Passerine (metalaxyl or mefenoxam)
    - 850.2300 Avian Reproduction, Mallard and bobwhite (metalaxyl)
    - 850.1075 Acute Freshwater Fish Toxicity with a TEP, Rainbow trout and bluegill (metalaxyl TEP and mefenoxam TEP)
    - 850.1010 Acute Freshwater Invertebrate Toxicity with a TEP, Waterflea (*Daphnia magna*) (metalaxyl TEP and mefenoxam TEP)
    - 850.1075 Acute Saltwater Fish Toxicity, Marine/estuarine fish (metalaxyl or mefenoxam)

- 850.1075 Acute Salwater Fish Toxicity with a TEP, on a marine/estuarine fish (metalaxyl TEP and mefenoxam TEP)
- 850.1025 Acute Marine/Estuarine Bivalve Toxicity, Oyster (metalaxyl or mefenoxam)
- 850.1025 Acute Marine/Estuarine Bivalve Toxicity with a TEP, Oyster (metalaxyl TEP and mefenoxam TEP)
- 850.1035 Acute Marine Estuarine Bivalve Toxicity with a TEP, Mysid (metalaxyl TEP and mefenoxam TEP)
- 850.1075 Acute Freshwater Fish Toxicity, Fathead minnow (metalaxyl or mefenoxam)
- 850.1350 Saltwater Invertebrate Life Cycle, Mysid (metalaxyl or mefenoxam)
- 850.4100 Seedling Emergence with a TEP, Tier 1, on 10 crop species (metalaxyl TEP and mefenoxam TEP)
- 850.4150 Vegetative Vigor with a TEP, Tier 1, on 10 crop species (metalaxyl TEP and mefenoxam TEP)
- 850.5400 Aquatic Plant Growth, Algae, Tier 1, on blue-green alga (e.g., *Anabaena flos-aquae*), freshwater diatom (e.g., *Navicula pelliculosa*), and marine diatom (e.g., *Skeletonema costatum*) (metalaxyl or mefenoxam)

- Please refer to *Registration Review–Preliminary Problem Formulation for Environmental Fate, Ecological Risk, and Endangered Species for Metalaxyl (PC Code 113501) and Mefenoxam (aka metalaxyl-M, PC Code 113502),* dated August 27, 2009, located in docket EPA-HQ-OPP-2009-0863 on the internet at www.regulations.gov, for a detailed discussion of the anticipated ecological risk assessment needs.

Human Health Risk:

- A human health risk assessment for metalaxyl was conducted in support of the 1994 metalaxyl RED. In that assessment, the Agency found no risks of concern.

- The toxicology data on metalaxyl and mefenoxam were evaluated in 1997. EPA concluded that data on mefenoxam and metalaxyl demonstrated similar toxicity and that metalaxyl data can be used to support the mefenoxam toxicity database.

- The most recent human health risk assessment for mefenoxam was completed in May 2007. In that assessment, the Agency found no risks of concern.

- The most recent drinking water assessment was completed in 2007 for mefenoxam. In that assessment, the Agency found no risks of concern.

- The 2007 drinking water assessment for mefenoxam also concluded that the environmental fate and transport properties of metalaxyl and mefenoxam are equivalent. Therefore, while most of the data were generated using metalaxyl, the results are relevant for mefenoxam as well.

- The tolerance expressions for metalaxyl in [40 CFR §180.408] and for mefenoxam in [40 CFR §180.546] will be reviewed during registration review to ensure that they appropriately cover the metabolites and degradates of metalaxyl and mefenoxam and that they specify the residues to be measured for each commodity. At this time, the Agency expects that any proposed revisions would be to the chemical description rather than the individual tolerance levels.

- Additional residue data for cottonseed and tomato paste have been submitted to the Agency in response to the metalaxyl RED Data Call-In (DCI). The Agency anticipates reviewing these studies during registration review.

- A number of tolerance actions (nomenclature changes, revocations, and modifications) remain outstanding from the Metalaxyl RED. The Agency anticipates addressing these tolerance actions during registration review.

- The Agency anticipates conducting new dietary (food and drinking water) exposure and residential exposure risk assessments for metalaxyl during registration review. The Agency also anticipates conducting new occupational handler exposure risk assessments for both metalaxyl and mefenoxam during registration review.

- The toxicity database is complete with the exception of the following guideline data, which the Agency anticipates requiring in order to conduct the planned human health risk assessments for the registration review of metalaxyl and mefenoxam:
  - 870.6200 Neurotoxicity Battery, Acute and Subchronic Studies (mefenoxam)
  - 870.7800 Immunotoxicity (mefenoxam)

- Please refer to *Metalaxyl/Mefenoxam. Human Health Assessment Scoping Document in Support of Registration Review,* dated December 7, 2009, located in docket EPA-HQ-OPP-2009-0863 on the internet at www.regulations.gov, for a detailed discussion of the anticipated human health risk assessment needs.

Other Data Needs:

- The Agency anticipates requiring the following guideline data:

  - 830.7050 UV/Visible Light Absorption (metalaxyl and mefenoxam)

Endocrine Disruptor Screening Program

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (EDSP) to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a

chemical substance to interact with the estrogen, androgen, and or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine related effects caused by the substance, and establish a quantitative relationship between the dose and the E, A, or T effect.

Between October 2009 and February 2010, EPA is issuing test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. This list of chemicals was selected based on the potential for human exposure through pathways such as food and water, residential activity, and certain post-application agricultural scenarios. This list should not be construed as a list of known or likely endocrine disruptors.

Metalaxyl is among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

Mefenoxam is not among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. Under FFDCA sec. 408(p) the Agency must screen all pesticide chemicals. Accordingly, EPA anticipates issuing future EDSP orders/data call-ins for all Registration Review cases, including those for which EPA has already opened a Registration Review docket for a pesticide active ingredient.

Timeline

The projected timeline for the completion of the metalaxyl and mefenoxam registration review is presented in Table 1.

Table 1. Projected Metalaxyl and Mefenoxam Registration Review Timeline

Activity	Estimated Date
Opening the docket	
Open Registration Review Docket and Open Public Comment Period	2009 December
Close Public Comment Period	2010 February
Case Development	
Develop Final Work Plan (FWP)	2010 May
Issue DCI	2011 January - March
Data Submission	2013 January - March
Complete Preliminary Risk Assessments and Open Public Comment Period	2014 July - September
Close Public Comment Period	2014 October - December
Registration Review Decision	
Develop Proposed Registration Review Decision and Open Public Comment Period	2015 January - March
Close Public Comment Period	2015 April - June
Complete Final Registration Review Decision and Begin Post-Decision Follow-up	2015
Total (years)	6

Guidance for Commenters

The public is invited to comment on EPA's preliminary registration review work plan and rationale. The Agency will carefully consider all comments, as well as any additional information or data provided in a timely manner, prior to issuing a final work plan for the metalaxyl and mefenoxam case.

Through the registration review process, the Agency intends to solicit information on trade irritants and, to the extent feasible, take steps toward facilitating irritant resolution. Growers and other stakeholders are asked to comment on any trade irritant issues resulting from lack of Maximum Residue Levels (MRL) or disparities between U.S. tolerances and MRLs in key export markets, providing as much specificity as possible regarding the nature of the concern.

Metalaxyl and mefenoxam are not identified as causes of impairment for any water bodies listed as impaired under section 303(d) of the Clean Water Act, based on information provided at http://iaspub.epa.gov/tmdl_waters10/attains_nation_cy.cause_detail_303d?p_cause_group_id=885. In addition, no Total Maximum Daily Loads (TMDL) have been developed for metalaxyl or mefenoxam, based on information provided at http://iaspub.epa.gov/tmdl_waters10/attains_nation.tmdl_pollutant_detail?p_pollutant_group_id=885&p_pollutant_group_name=PESTICIDES. More information on impaired water bodies and TMDLs can be found at http://www.epa.gov/owow/tmdl/. The Agency invites submission of water quality data for these pesticides. To the extent possible, data should conform to the quality standards in Appendix A of the *OPP Standard Operating Procedure: Inclusion of Impaired Water Body and Other Water Quality Data in OPP's Registration Review Risk Assessment and Management Process* (see: http://www.epa.gov/oppfead1/cb/ppdc/2006/november06/session1-sop.pdf), in order to ensure they can be used quantitatively or qualitatively in pesticide risk assessments.

EPA seeks to achieve environmental justice, the fair treatment and meaningful involvement of all people, regardless of race, color, national origin, or income, in the development, implementation, and enforcement of environmental laws, regulations, and policies. To help address potential environmental justice issues, the Agency seeks information on any groups or segments of the population who, as a result of their location, cultural practices, or other factors, may have atypical, unusually high exposure to metalaxyl or mefenoxam, compared to the general population. Please comment if you are aware of any sub-populations that may have atypical or unusually high exposure compared to the general population.

Stakeholders are also specifically asked to provide information and data that will assist the Agency in refining the risk assessments, including any species-specific ecological effects determinations. The Agency is interested in obtaining the following information:

1. Confirmation of the following label information:
    a. sites of application
    b. formulations
    c. application methods and equipment

    d. maximum application rates in units related to mass per unit area of treatment zone
    e. frequency of application, application intervals, and maximum number of applications per season
    f. geographic limitations on use.
2. Use or potential use distribution (*e.g.*, geographical distribution of relevant uses).
3. Use history.
4. Median and 90th percentile reported use rates from usage data – national, state, and county.
5. Application timing (date of first application and application intervals) by use – national, state, and county.
6. Sub-county use site data.
7. Usage/use information for non-agricultural uses (*e.g.*, warehouses, railroad cars, domestic dwellings).
8. Directly acquired county-level usage data (not derived from state level data).
    a. maximum reported use rate from usage data – county
    b. median and 90th percentile number of applications – county
    c. total pounds per year – county
    d. the year the pesticide was last used in the county/sub-county area
    e. the years in which the pesticide was applied in the county/sub-county area
9. Typical application interval (days).
10. State or local use restrictions.
11. Ecological incidents (non-target plant damage and avian, fish, reptilian, amphibian and mammalian mortalities) not already reported to the Agency.
12. Monitoring data.

Next Steps

After the 60-day public comment period closes, the Agency will review and respond to any comments received in a timely manner, and then issue a Final Work Plan for the metalaxyl and mefenoxam case.

II. FACT SHEET – Metalaxyl and Mefenoxam Registration Review

Background Information

- Metalaxyl and Mefenoxam Registration Review Case Number: 0081.
- Metalaxyl Pesticide Chemical (PC) Code: 113501.
- Metalaxyl Chemical Abstracts Service (CAS) Number: 57837-19-1.
- Metalaxyl was first registered in the U.S. in 1979. The Metalaxyl Reregistration Eligibility Decision document (RED) was signed in September 1994. Product reregistration for metalaxyl was completed in December 2006.
- Mefenoxam PC Code: 113502.
- Mefenoxam CAS Number: 70630-17-0.
- Mefenoxam was first registered in the U.S. in 1992. Since mefenoxam was first registered after 1984, it was not subject to reregistration; therefore, there is no RED for mefenoxam.
- Currently, the technical registrants for metalaxyl are Drexel, Nations Ag, and LG LifeSciences and the technical registrants for mefenoxam are Syngenta and LG LifeSciences.
- Currently, there are 133 active metalaxyl registrations and 73 active mefenoxam registrations (including Section 3 and Special Local Need Section 24 (c) registrations).
- Pesticide Re-Evaluation Division (PRD) Contact: Katie Weyrauch (weyrauch.katie@epa.gov).
- Registration Division (RD) Contacts: Mary Waller (waller.mary@epa.gov); Tamue Gibson (gibson.tamue@epa.gov).

Use & Usage Information

- Metalaxyl and mefenoxam are systemic fungicides that are registered for use to control foliar (plant) and soil diseases. These ingredients are effective against soil-borne diseases caused by *Pythium* and *Phytophthora* and foliar diseases caused by the *Phycomycetes* (downy mildews).

- Some of the target pests include certain types of white rust, blue mold, downy mildew, basal stem rot, black shank, collar rot, crown rot, foot rot, fruit rot, heart rot, leather rot, red stele, root rot, stem rot, trunk canker, damping-off, leak root rot, seed rot, and seedling disease complex.

- Metalaxyl and mefenoxam may be used as foliar, soil, or seed treatments for agricultural crops or as a treatment in the residential environment.

- Formulation types include granular, wettable powder, dust, emulsifiable concentrate, dry flowable concentrate, water soluble powder, wettable soluble packets, crystalline, and liquid ready-to-use products.

- Application methods include multiple foliar or soil incorporation, surface spraying (broadcast or band), drenching, sprinkler or drip irrigation, soil mix, and seed treatment.

- End-use products are registered for use on a variety of terrestrial food, feed, and nonfood crops (including both field crops and orchards); on greenhouse nonfood crops; and as a seed treatment for certain crops. These registered uses also include some residential uses on lawns and landscape areas around residential buildings.

- Overall, the largest agricultural uses, in terms of pounds of active ingredient used per acre (lbs a.i./A), are potatoes, oranges, tobacco, tomatoes, carrots, spinach, cotton, lettuce, onion, and soybean. Metalaxyl and mefenoxam have several nonfood ornamental uses as well, including lawns, golf courses, and nurseries. Mefenoxam also has a forestry use. Use data are not available for non-agricultural use sites.

Recent Actions

- A petition concerning grape, potato, and leafy vegetables is currently under review in EPA. The petitioner wants to add grapes to the Ridomil Gold SL label (EPA Reg. No. 100-1202) as it already exists on another label, to change the potato rate in the directions for use from 0.188 to 0.34 lb a.i./acre, and to expand the head and leaf lettuce uses.

Ecological Risk Assessment Status

Please refer to *Registration Review: Preliminary Problem Formulation for Ecological Risk, Environmental Fate, Endangered Species, and Drinking Water Assessments for Metalaxyl and Mefenoxam*, dated August 27, 2009, located in docket EPA-HQ-OPP-2009-0863 on the internet at www.regulations.gov, for a discussion of the key findings of the most recent ecological risk assessment for metalaxyl and mefenoxam.

Summary of Risks – Metalaxyl:

- In the 1994 metalaxyl RED, the Agency concluded that metalaxyl and its degradation product are mobile and persistent. Based on mobility, persistence, and groundwater monitoring data, metalaxyl has the potential to cause ground water contamination.

- In the RED, the Agency reviewed data on the toxicity of metalaxyl to nontarget animals and plants. Metalaxyl was characterized as practically nontoxic to birds on a subacute dietary basis, slightly toxic to birds on an acute oral basis, slightly toxic to mammals on an acute oral basis, practically nontoxic to freshwater fish, slightly toxic to freshwater invertebrates, slightly toxic to saltwater crustaceans, moderately toxic to saltwater mollusks, and practically nontoxic to bees. Toxicity to aquatic plants was characterized as low. Avian reproduction data were not available. Testing with formulated products containing metalaxyl as the active ingredient found that they were in some cases more acutely toxic than the active ingredient.

- In the ecological risk assessment in the RED, the Agency concluded that none of the terrestrial and aquatic risks to nontarget organisms assessed exceed the Agency's level of concern.

- Because risk to all types of nontarget organisms was determined to be low, the Agency did not find in the RED that any risk mitigation was needed to protect nontarget organisms. Risk mitigation was specified, however, to minimize the potential risk for metalaxyl to contaminate groundwater. The RED specified a number of measures to reduce this risk, including groundwater advisory, environmental hazard, and spray drift advisory statements on end-use product labels, and the development of a user education program if registrants detect groundwater levels at or above 400 ppb in samples from monitoring sites.

Summary of Risks – Mefenoxam:

- In the 2001 ecological risk assessments for proposed new mefenoxam uses on canola seed and on several fruits, vegetables, and herbs, the Agency concluded that mefenoxam is mobile and persistent in the terrestrial and aquatic environment.

- In the 2001 ecological risk assessments for proposed new mefenoxam uses on canola seed and on several fruits, vegetables, and herbs, the Agency reviewed data on the toxicity of mefenoxam to nontarget animals and plants. Mefenoxam was characterized as slightly toxic to birds on a subacute dietary basis, slightly toxic to birds on an acute oral basis, practically nontoxic to bees, practically nontoxic to freshwater fish, practically nontoxic to freshwater crustaceans, and moderately toxic to saltwater mollusks. Toxicity to aquatic plants was characterized as low. Data on chronic toxicity to fish and chronic toxicity to invertebrates were not available for mefenoxam, but were assumed to be equivalent to the chronic toxicity observed in tests with metalaxyl.

- The Agency also concluded that the canola seed treatment use was not anticipated to pose risks to any endangered or threatened species. However, acute and chronic risk to saltwater fish, chronic risk to saltwater invertebrates, and risk to terrestrial plants could not be evaluated because toxicology data on these species were not available.

- In the 2001 ecological risk assessment for proposed new mefenoxam uses on several fruits, vegetables, and herbs, the Agency identified some risks of concern for acute toxicity to both small and larger mammals, including to threatened and endangered species. Chronic risks to both small and larger mammals, however, did not exceed the Agency's level of concern. The assessment also concluded that acute and chronic risk to freshwater fish, acute and chronic risk to aquatic invertebrates, and acute risk to saltwater invertebrates did not exceed the Agency's level of concern. However, acute and chronic risk to saltwater fish and chronic risk to saltwater invertebrates could not be evaluated because toxicology data on these species were not available.

- In the 2007 drinking water assessment for mefenoxam, the Agency found no risks of concern. This assessment also concluded that the environmental fate and transport properties of metalaxyl and mefenoxam are equivalent. Therefore, while most of the data were generated using metalaxyl, the results are relevant for mefenoxam as well.

Human Health Risk Assessment Status

Please refer to the document *Metalaxyl/Mefenoxam: Human Health Assessment Scoping Document in Support of Registration Review*, dated December 7, 2009, located in docket EPA-HQ-OPP-2009-0863 on the internet at www.regulations.gov, for a discussion of the key findings of the most recent human health risk assessment for metalaxyl and mefenoxam.

Hazard Characterization – Metalaxyl and Mefenoxam:

- The toxicology data on metalaxyl and mefenoxam were evaluated in 1997. EPA concluded that data on mefenoxam and metalaxyl demonstrated similar toxicity and that metalaxyl data can be used to support the mefenoxam toxicity database.

- Toxicology data for metalaxyl and mefenoxam indicate that the major target organ is the liver. Liver effects observed in subchronic oral studies in the rat, mouse, and dog include increased liver enzymes, increased incidence of pathological observations in the liver, and increased liver weights.

- In acute toxicity studies, metalaxyl is Toxicity Category III through the acute oral exposure route and the acute dermal exposure route. Because metalaxyl cannot be prepared and tested in a respirable form, the requirement for an acute inhalation study was waived by the Agency. Metalaxyl is Toxicity Category IV through the dermal irritation route and Toxicity Category II through the eye irritation route. It is not a dermal sensitizer.

- The only difference in toxicity between metalaxyl and mefenoxam appears to occur in rat developmental studies. No developmental toxicity was observed in mefenoxam-treated rats, whereas developmental toxicity and marked maternal toxicity were observed in metalaxyl-treated rats.

- The toxicology data for metalaxyl and mefenoxam do not indicate reproductive toxicity.

- While there are no acute or subchronic neurotoxicity studies available for metalaxyl and mefenoxam, data from other studies in the database demonstrate no neurotoxicity, nor clinical signs of neurotoxic potential.

- Metalaxyl and mefenoxam are not mutagenic. Metalaxyl has been classified as "not likely to be a human carcinogen." Based on the classification of metalaxyl, mefenoxam is also considered "not likely to be a human carcinogen."

Summary of Risks – Metalaxyl and Mefenoxam:

Dietary (Food and Drinking Water)

- The most recent dietary exposure assessment was conducted for mefenoxam in 2007 and covered the food uses of both metalaxyl and mefenoxam.

- Since there is no indication of an adverse effect attributable to a single dose, an acute dietary exposure assessment was not conducted.

- A chronic dietary (food and drinking water) exposure assessment was conducted. Dietary risk estimates for metalaxyl and mefenoxam were below the Agency's level of concern for the general U.S. population and all population subgroups.

Residential

- The most recent residential risk assessment was conducted for mefenoxam in 2007 and covered the residential uses of both metalaxyl and mefenoxam.

- No hazard from the dermal route of exposure was identified. Therefore, only inhalation exposure and incidental oral exposure assessments were conducted.

- None of the assessed residential handler and postapplication exposure risks exceeded the Agency's level of concern.

Aggregate

- The 2007 human health risk assessment for mefenoxam included an aggregate exposure risk assessment. The mefenoxam aggregate risk assessment also covered the uses of metalaxyl.

- No appropriate endpoint attributable to a single dose was identified; therefore, an acute aggregate risk assessment was not conducted.

- Aggregate assessments were conducted for short-term, intermediate-term, and chronic exposure durations. None of the assessed aggregate exposure risks exceeded the Agency's level of concern.

Occupational

- There is potential for short-term and intermediate-term occupational handler exposure to metalaxyl and mefenoxam during mixing, loading, and applying activities. No previous occupational handler exposure risk assessments have been conducted for metalaxyl. Toxicological endpoints for mefenoxam were established in April 2000. The Agency has conducted occupational handler exposure risk assessments for a number of mefenoxam

uses and exposure scenarios. In those assessments, none of the assessed scenarios for handler exposure exceeded the Agency's level of concern. The hazards and endpoints are identical for metalaxyl and mefenoxam; therefore, the occupational handler risk assessments conducted for mefenoxam uses and exposure scenarios are sufficient to cover similar metalaxyl uses and exposure scenarios as well.

- There are many possible occupational handler exposure scenarios for metalaxyl and mefenoxam. For both metalaxyl and mefenoxam, a number of exposure scenarios for some uses have not been specifically assessed in previous risk assessments. Due to the conservative approach to risk assessment, most of these unassessed handler exposure scenarios are expected to be covered by those that have been assessed (i.e., the maximum application rates are comparable to other use pattern scenarios that resulted in MOEs greatly exceeding the Agency's level of concern). However, there are a few occupational handler exposure scenarios that may not be covered by previous assessments. The Agency anticipates conducting new occupational handler risk assessments for metalaxyl and mefenoxam during registration review.

- Occupational postapplication exposure can occur through the dermal and/or inhalation route. However, short-term and intermediate-term dermal toxicity endpoints were not identified and inhalation exposure during postapplication activities was considered negligible for all metalaxyl and mefenoxam use scenarios; therefore, a risk assessment for postapplication activities was not considered necessary.

- Metalaxyl is among several agricultural chemicals included in the Agricultural Health Study (AHS). The AHS began in 1993 and is a collaboration of the National Institute of Environmental Health Sciences (NIEHS), the National Cancer Institute (NCI), the EPA, and the National Institute for Occupational Safety and Health (NIOSH). Designed as a large long-term epidemiological study, the AHS collects and analyzes data on the health and work practices of nearly 90,000 farmers and their families in Iowa and North Carolina who enrolled in the study before any disease developed. The study focuses particularly on farmers' exposure to 50 chemicals including many of the most widely used pesticides. As data are collected over a period of years, scientists can compare overall health outcomes for people who differ in whether they have had exposure to various chemicals. While these comparisons cannot conclusively demonstrate how exposure affects health, they can show some statistical associations. More information on the AHS can be found at: http://aghealth.nci.nih.gov.

<u>Cumulative</u>

- Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to metalaxyl/mefenoxam and any other substances, and metalaxyl/mefenoxam do not appear to produce a toxic metabolite produced by other substances. For the purposes of this assessment, therefore, EPA has not assumed that metalaxyl/mefenoxam have a common mechanism of toxicity with other substances. For information regarding

EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

Human Studies

- Past metalaxyl and mefenoxam risk assessments rely in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their dermal and inhalation exposure. Many such studies, involving exposure to many different pesticides, comprise generic pesticide exposure databases such as the Pesticide Handlers Exposure Database (PHED) and the Agricultural Reentry Task Force (ARTF) Database. The Agency has reviewed all the studies in these multi-pesticide generic exposure databases, and on the basis of available evidence has found them to have been neither fundamentally unethical nor significantly deficient relative to standards of ethical research conduct prevailing when they were conducted. There is no regulatory barrier to continued reliance on these studies, and all applicable requirements of the Agency's Rule for the Protection of Human Subjects (40 CFR Part 26) have been satisfied.

Incident Reports

Ecological Incidents:

- In August 2009, an updated review of metalaxyl and mefenoxam incident reports was prepared by consulting Ecological Incident Information System (EIIS), which is maintained by the EPA Office of Pesticide Programs, and the Avian Incident Monitoring System (AIMS), which is maintained by the American Bird Conservancy. EIIS and AIMS were searched for ecological incidents involving metalaxyl and mefenoxam in the U.S. During the time period captured in the report, eight ecological incidents apparently involved products containing metalaxyl and/or mefenoxam. Four of these incidents reported adverse field effects to nontarget organisms (fish). There were also four incidents of possible crop damage associated with application. However, evidence was lacking to conclusively link the reported effects to exposure to metalaxyl or mefenoxam. Also, in one of these incidents, the application of these pesticides was reported to be in violation of the pesticide labels.

Human Health Incidents:

- In June and July 2009, updated reviews of metalaxyl and mefenoxam human health incident reports were prepared by consulting the OPP Incident Data System (IDS) for reports of poisoning incidents in the U.S. from 2002 to present. IDS includes reports of incidents from various sources, including mandatory FIFRA Section 6 (a) (2) reports from registrants, other federal and state health and environmental agencies, and individual consumers. There were a relatively low number of incidents reported to the

OPP IDS, including one incident that apparently involved metalaxyl and 66 incidents that apparently involved mefenoxam. Overall, the severity of these incidents was low and there was no apparent trend over time. Only one incident was classified as major and there were no deaths reported. Most of the incidents (65 of the metalaxyl/mefenoxam incidents) involved the product 'Apron XL XS/Apron treated Grass Seed,' and many incidents noted dermal effects that may be indicative of irritation, such as rash, hives, welts, pruritis (intense itching), or erythema (redness of the skin). The Agency anticipates further evaluating the potential association of metalaxyl and mefenxoam with dermal irritation incidents during the development of the human health risk assessment for registration review.

Data Call-In (DCI) Status

- The Agency anticipates reviewing the following studies, which were submitted in response to the metalaxyl RED DCI, during registration review:
    - 860.1500 Crop Field Trials (Cotton) – MRID 44208103
    - 860.1520 Processed Food/Feed (Tomato) – MRID 44208104 and 44208105

Tolerances and International Harmonization

Metalaxyl:

- Tolerances are established under 40 CFR 180.408(a) for the combined residues of metalaxyl [*N*-(2,6-dimethylphenyl)-*N*-(methoxyacetyl)alanine methyl ester], its metabolites containing the 2,6-dimethylaniline moiety, and *N*-(2-hydroxymethyl-6-methylphenyl)-*N*-(methoxyacetyl)-alanine methyl ester, each expressed as metalaxyl equivalents, in/on various plant and livestock commodities at levels ranging from 0.02 to 25 ppm. In addition, a tolerance with regional registration has been established under 180.408(c) for papaya at 0.1 ppm, and tolerances for indirect or inadvertent residues of metalaxyl are established under 180.408(d) for barley, cereal grain, oat, and wheat commodities ranging from 0.2 ppm (grain) to 2.0 ppm (fodder, forage, and straw).

Mefenoxam:

- Tolerances for residues of mefenoxam are established under 40 CFR 180.546(a) for the combined residues of (*R*)- and (*S*)-2-[(2,6-dimethyl(phenyl)-methoxyacetylamino]-propionic acid methyl ester, its metabolites containing the 2,6 dimethylaniline moiety, and *N*-(2-hydroxymethyl-6-methylphenyl)-*N*-(methoxyacetyl)alanine methyl ester, each expressed as mefenoxam equivalents, in/on globe artichoke, minor or tropical fruits, and herbs at levels ranging from 0.05 ppm to 55 ppm.

Tolerance Expression – Compliance/Measurement Policy:

- HED recommends modification of the tolerance expressions for both metalaxyl and mefenoxam according to the new compliance/measurement policy as follows:

  > Tolerances are established for residues of metalaxyl, including its metabolites and degradates, in or on a number of commodities. Compliance with the tolerance levels specified is to be determined by measuring only the combined residues of metalaxyl [*N*-(2,6-dimethylphenyl)-*N*-(methoxyacetyl)alanine methyl ester], its metabolites containing the 2,6-dimethylaniline moiety, and *N*-(2-hydroxymethyl-6-methylphenyl)-*N*-(methoxyacetyl)-alanine methyl ester, each expressed as the stoichiometric equivalent of metalaxyl.

- Tolerances are established for residues of mefenoxam, including its metabolites and degradates, in or on a number of commodities. Compliance with the tolerance levels specified is to be determined by measuring only the combined residues of (*R*)- and (*S*)-2-[(2,6-dimethyl(phenyl)-methoxyacetylamino]-propionic acid methyl ester, its metabolites containing the 2,6 dimethylaniline moiety, and *N*-(2-hydroxymethyl-6-methylphenyl)-*N*-(methoxyacetyl)alanine methyl ester, each expressed as the stoichiometric equivalent of mefenoxam.

- A table listing the differences between U.S. tolerances, Canadian, and CODEX MRLs for metalaxyl and mefenoxam is included in the *Metalaxyl/Mefenoxam: Human Health Assessment Scoping Document in Support of Registration Review*. For those tolerances and MRLs that are not harmonized, the Agency will determine the feasibility of harmonization during registration review.

Labels

Labels can be obtained from the Pesticide Product Label System (PPLS) website: http://oaspub.epa.gov/pestlabl/ppls.home.